REMARKS

Amendments to the Specification

The specification has been amended to remove embedded hyperlinks. No new matter has been added.

Amendments to the Claims

Claims 22-49 were pending. Claims 22-32 have been canceled without prejudice. Claims 33, 35, 36, 38, 41-44 and 47 have been amended. New claims 50-59 have been added. Therefore, claims 33-59 are pending.

The method of claim 33 has been amended to specify a monoclonal antibody which binds to the "human macrophage mannose receptor (MMR)" and a cytotoxic T cell response (CTL) "mediated by both $CD4^+$ and $CD8^+$ T cells." Support for this amendment can be found throughout the application as originally filed, for example, page 3, lines 16-24.

Claim 35 has been amended to specify that the antigen presenting cells are dendritic cells. Support for this amendment can be found throughout the application as originally filed, for example, page 7, line 38 through page 8, line 2.

Claim 36 has been amended to correct a typographical error.

Claim 38 has been amended to specify that the antigen is β human chorionic gonadotropin. Support for this amendment can be found throughout the application as originally filed, for example, page 5, lines 15-20.

Claims 41-43 have been amended to specify that the CDR amino acid sequences include conservative "sequence" modifications. Support for these amendments can be found throughout the specification as originally filed, for example, at page 13, lines 1-20.

Claim 44 has been amended without prejudice to delete reference to "sufficiently homologous" sequence. Claim 44 has been further amended to include reference to conservative sequence modification of the recited heavy and light chain variable region amino acid sequences. Support for this amendment can be found throughout the specification as originally filed, for example, at page 13, lines 1-20.

Claim 47 has been amended to depend from claim 35.

New claim 50 is drawn to a method of inducing or enhancing a T cell mediated immune response against an antigen, which includes contacting a molecular conjugate, comprising a monoclonal antibody that binds to the human MMR linked to the antigen, with APCs such that

the antigen is processed and presented to T cells in a manner which induces or enhances a T cell-mediated response mediated by both $CD4^+$ and $CD8^+$ T cells against the antigen. Support for new claim 50 can be found throughout the application as originally filed, for example, in original claim 22 and a page 3, lines 25-37.

New dependent claims 51-58 further define the method of claim 50 and are identical to original claims 24-31, respectively.

New claim 59 is drawn to a method of immunizing a subject by administering a molecular conjugate comprising a monoclonal antibody that binds to the human MMR linked to an antigen, such that the molecular conjugate induces or enhances a CTL response mediated by both $CD4^+$ and $CD8^+$ T cells against the antigen. Support for new claim 59 can be found throughout the application as originally filed, for example, in original claim 32 and a page 3, lines 25-37 and at page 30, lines 20-21.

The foregoing claim amendments should in no way be construed as acquiescence to any of the Examiner's rejections and were made solely to expedite prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s). No new matter has been added.

Rejection of Claims 41-44 Under 35 U.S.C. §112, First Paragraph

Claims 41-44 are rejected as not being enabled. Specifically, the Examiner states that the specification "does not reasonably provide enablement for any antibody comprising 'conservative modifications thereof' or 'substantially homologous to' the SEQ ID NOs disclosed in claims 41-44."

Applicants respectfully traverse this rejection. First, Applicants note that the claims have been amended without prejudice to delete reference to amino acid sequences which are "sufficiently homologous." Accordingly, this aspect of the rejection is moot.

As amended, claims 41-44 encompass antibodies which bind to the human MMR having particular CDR and variable region amino acid sequences, and conservative sequence modifications of these CDR sequences. Conservative amino acid substitutions within the CDR domains that do not remove the antibody's ability to bind are fully enabled based on Applicants' specification and the skill of the art at the time of the invention.

As explicitly taught in the present specification (see, *e.g.*, page 13, lines 1-20), and as was known in the art at the time of the present invention, "conservative sequence modifications"

in the context of antibody sequences refer to modifications that do not substantially affect antibody binding. It was also well-known that "conservative sequence modifications" include particular art-recognized amino acid substitutions having a similar side chain. Such amino acid residues having similar side chains are clearly defined in the present specification (see, *e.g.*, page 13, lines 1-20) and were well known in the art as evidenced by, for example, Stryer, *Biochemistry*, 2nd ed., Chapter 2, pages 13-15 (attached as Appendix A). Moreover, routine techniques for testing whether such conservative substitutions within the heavy and light chain variable regions affect or remove the binding activity of a given antibody were also well known and within the skill of the art (see, *e.g.*, Example 3 describing the binding characteristics of the βhCG-B11 and B11sfv-βhCG constructs which include human anti-MMR antibodies). Therefore, the presently claimed conservative amino acid substitutions within the recited CDR and variable regions are fully enabled.

Indeed, Applicants respectfully note that antibody variable and CDR regions are relatively short sequences. Given their short length, combined with the knowledge and high level of skill in the antibody art at the time of the invention, one of ordinary skill in the art clearly could have identified and made conservative sequence substitutions within the claimed variable region and CDR sequences which do not remove binding, without undue experimentation. Moreover, it was also well known in the art that CDR residues critical for binding could be identified by comparing the antibody heavy and light chain variable region sequences to their respective germline sequences to identify which residues were amenable to conservative modification and which were not, *i.e.*, which residues had been conserved and which had been somatically mutated to improve binding.

Accordingly, based on the knowledge and high level of skill in the art at the time of the present invention, and the relatively short sequences of the claims CDR and variable regions, it would not have been unpredictable, or have required undue experimentation, to have generated antibodies which retain APC binding having conservative sequence modifications within the presently claimed variable or CDR regions.

The Examiner relies on Rudikoff *et al.* in support of the position that "[e]ven minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding." However, this does not establish lack of enablement. Rudikoff *et al.* merely show that certain residues within antibody variable regions are critical for binding, not that it would have required undue experimentation or have been

outside the ordinary skill in the art at the time of the invention, to have identified such residues. Indeed, as discussed above, it was well within the skill of the art to have identified such residues, particularly within relatively short variable and CDR regions. Moreover, Rudikoff *et al.* describe studies in which non-conservative amino acid substitutions (*e.g.*, substitution of alanine for glutamic acid) were made within the variable heavy chain region, as opposed to conservative substitutions as presently claimed.

Applicants respectfully note that the question of whether certain amino acid modifications can affect the binding affinity of an antibody is not the relevant inquiry in the present case. The relevant inquiry is whether conservative sequence modifications as claimed are fully enabled, *i.e.*, whether one of ordinary skill at the time of the present invention could have identified and made such substitutions, without removing antibody binding and without undue experimentation. As discussed in detail above, given the high level of skill and knowledge in the art at the time of the present invention, combined with the teachings of Applicants' specification, one of ordinary skill in the art clearly would have achieved this.

Rejection of Claims 41-44 Under 35 U.S.C. §112, First Paragraph

Claims 41-44 are rejected as failing to comply with the written description requirement. The Examiner states that Applicants are "not in possession of any antibody comprising 'conservative modifications thereof' or 'substantially homologous to' the SEQ ID NOs disclosed in claims 41-44."

Applicants respectfully traverse this rejection. As noted above, the claims have been amended without prejudice to delete reference to amino acid sequences which are "sufficiently homologous." Accordingly, this aspect of the rejection is moot.

As amended, claims 41-44 are drawn to the method of claim 33, wherein the heavy and light chain variable regions of the human MMR antibody are defined by specific CDR3, CDR2, and CDR1 sequences. The present specification explicitly describes such antibodies which include conservative sequence modifications. For example, at page 4, lines 23-34, Applicants describe antibodies which comprise specific CDR and variable regions sequences, as well as conservative sequence modifications within these sequences. Applicants also clearly define such conservative modifications as referring to "modifications that do not substantially affect or alter the binding characteristics of the antibody containing the claimed amino acid sequence" (see, *e.g.*, page 13, lines 1-20) and include particular art-recognized amino acid substitutions having a

similar side chain. Such amino acid residues having similar side chains are also explicitly taught in the present specification and were well known in the art as evidenced by, for example, Stryer, *Biochemistry*, 2nd ed., Chapter 2, pages 13-15 (attached as Appendix A).

Thus, based on Applicants' description and the knowledge in the art, one of ordinary skill in the art would have recognized that Applicants had full possession of the claimed invention at the time of filing, *i.e.*, the claimed methods which employ particular antibodies defined by sequence that bind the human MMR, including conservative sequence modifications within the variable regions of these antibodies.

Indeed, it is firmly established that the descriptive text needed to meet the Written Description requirement varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005). In *Capon*, the Federal Circuit explained that "since the law is applied to each invention in view of the state of the relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science." *Id.* Specifically, the Court stated that:

> Precedent illustrates that the determination of what is needed to support generic claims to biological subject matter ***depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter.*** *Id.* at 1359 (emphasis added).

The Court further explained that "the written description may be satisfied 'if in the knowledge of the art the disclosed function is ***sufficiently correlated to a particular, known structure.***'" *Id.* (citing *Amgen Inc. v. Hoechst Marion Roussel*, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003) (emphasis added)). Accordingly, "[a]s each field evolves, the balance also evolves between what is known and what is added by each inventive contribution." *Id.* at 1358.

Based on the foregoing considerations and framework for written description articulated by the Federal Circuit, the subject matter of the presently pending claims (which encompass anti-APC human monoclonal antibodies that comprise particular CDR and/or variable regions sequences having conservative modifications) clearly meets the written description requirement under 35 U.S.C. §112, first paragraph.

First, with respect to the existing knowledge in the field at the time of the invention, the present specification and the enclosed publication (Stryer *et al.*) clearly show that it was well-known which amino acid residues shared similar side chains and, therefore, which amino acid

residues could likely be substituted "conservatively" for another residue without removing a protein's activity or function (*e.g.*, antigen-binding). In addition, the science with respect to testing antibody sequences for binding was highly mature. Indeed, routine techniques could be used to test whether such conservative substitutions within the heavy and light chain variable regions affected or removed the binding activity of a given antibody, *i.e.*, such techniques were well known and within the skill of the art (see, *e.g.*, Example 3 describing the binding characteristics of the βhCG-B11 and B11sfv-βhCG constructs which include human anti-MMR antibodies). Moreover, given the maturity of the science, the predictability of the technology for generating similar antibodies having conserved sequence modifications was also high.

Accordingly, for at least the foregoing reasons, it would have been clear to one of ordinary skill in the art that Applicants had full possession of the claimed invention at the time of filing. Applicants therefore respectfully request the Examiner to reconsider and withdraw this rejection under 35 U.S.C. §112, first paragraph.

Rejection of Claims 33-45 and 47-49 Under 35 U.S.C. §102(b)

Claims 33-45 and 47-49 are rejected as being anticipated by WO 01/85798. Specifically, the Examiner asserts that the '798 publication teaches an immune response mediated by MHC I/II complexes.

Applicants respectfully traverse this rejection. As amended, the method of claim 33 relates to a cytotoxic T cell response "mediated by both $CD4^+$ and $CD8^+$ T cells." Applicants were the first to demonstrate such a cytotoxic T cell effect. In fact, the particularly claimed method which induces or enhances a specific type of cytotoxic T cell response, as mediated through the human MMR by both MHC Class I and Class II pathways, was not predictable based on the teachings of the prior art (as described in detail below). Indeed, as described in the present specification (see, *e.g.*, Example 4), Applicants were the first to induce efficient CTL activity and, specifically, CTL activity directed towards an antigen using an antibody directed against the human MMR as claimed.

As was known in the art at the time of filing, dendritic cells (which express the mannose receptor bound by the molecular conjugate encompassed by the claims) are specialized cells of the immune system. Dendritic cells are the principle antigen presenting cells involved in primary immune responses. Their major function is to obtain antigen in tissues, migrate to lymphoid organs and activate T cells. Dendritic cells are capable of evolving from immature,

antigen-capturing cells to mature, antigen-presenting, T cell-priming cells; converting antigens into immunogens and expressing molecules such as cytokines, chemokines, costimulatory molecules and proteases to initiate an immune response.

At the time the present application was filed, the prior art had not shown that CTL responses mediated by both MHC Class I and Class II pathways could have been achieved. Indeed, immune responses achieved in the prior art were limited to those mediated by MHC Class II presentation to CD4 helper T cells. Helper T cells, in general, do not have any direct cytotoxic activity and, thus, achieving enhanced CD4 responses (*i.e.*, MHC Class II) alone would not have provided motivation to one of ordinary skill in the art to have tried developing a therapeutic immunization strategy, *e.g.*, for cancers or other disorders. This is true in particular for intracellular antigens (see, *e.g.*, claim 46), such as Pmel-17, for which a cytolytic T cell response (as taught by Tuting *et al.* (1998; Appendix B)) is critical for the cytolytic effect. In order to generate CTL responses that are mediated by both pathways, the antigen must be presented by the antigen presenting cell on MHC Class I molecules, which the prior art had not shown. Moreover, the intracellular pathways for MHC Class II and Class I presentation are completely distinct, and one can not extrapolate from the data of the prior art which pertains to enhancement of MHC Class II presentation, that targeting to the mannose receptor would also enhance MHC Class I presentation, and thereby CTL responses. Thus, the prior art would not have motivated one of ordinary skill in the art to have used an antibody against human MMR to elicit a CTL response mediated by both MHC Class I and Class II pathways, which are critical for effective vaccines.

As mentioned above, Applicants were the first to demonstrate that the generation a CTL response mediated by both MHC Class I and Class II pathways was possible by using an antibody targeted to the human MMR. Indeed, the prior art including the cited reference, WO 01/85798, fails to exemplify the claimed methods or show that it was predictable to induce such a CTL response. Therefore, the presently claimed invention is novel and Applicants respectfully request withdrawal of the present rejection.

Rejection of Claims 22-33 and 46 Under 35 U.S.C. §103(a)

Claims 22-33 and 46 are rejected as being unpatentable over WO 01/85798 in view of US 5,869,057. Applicants respectfully traverse this rejection. Notwithstanding, claims 22-33 have been canceled without prejudice. To the extent that this rejection pertains to claim 46,

Applicants refer to their arguments immediately above (the substance of which is reiterated here).

Double Patenting

Claims 22, 32 and 33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 39-44 of co-pending application, USSN 10/903191.

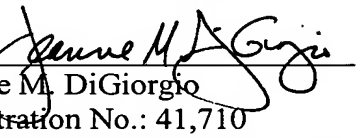
Applicants respectfully traverse this rejection. Notwithstanding, to expedite prosecution, Applicants will submit a terminal disclaimer upon the indication of allowable subject matter, if appropriate.

SUMMARY

Based on the foregoing amendments and arguments, reconsideration and withdrawal of all the rejections and allowance of this application with all pending claims are respectfully requested. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Dated: June 29, 2006

Respectfully submitted,

By 

Jeanne M. DiGiorgio
Registration No.: 41,710
LAHIVE & COCKFIELD, LLP
28 State Street
Boston, Massachusetts 02109
(617) 227-7400
(617) 742-4214 (Fax)
Attorney For Applicants